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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,099	03/19/2004	Chunhui Xu	099/004P	7715

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,099	XU ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-10 are under consideration. Claims 1, 3, 4, 6, and 8-10 are amended and claims 11-16 are canceled by amendment, filed 1/22/2007. Claims 1-10 are under consideration.

Priority

2. Applicant has not complied with conditions for receiving benefit of an earlier filing date for claims 11-16 and therefore the filing date (3/19/2004) was the effective filing date for these claims. Applicant traversed this non-compliance, however, Applicant canceled claim 11-16, to which the non-compliance pertained. Therefore, this issue of non-compliance is withdrawn.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 1/17/2006 was filed after the mailing date of the Office Action on 7/13/2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

4. The disclosure was objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant removed the hyperlinks by amendment to the specification, filed 12/13/2006. Therefore, the objection is withdrawn.

Claim Objections

5. Claim 1, objected to for reciting in b) "differentiate into areas", has been amended and no longer contains this recitation. Therefore, the objection is withdrawn.

Claims 9 and 10 were object to for reciting "a medium containing" whereas this should recite "a medium comprising". Applicant traversed this rejection on the grounds that "containing" is open claim language and therefore is appropriate. Applicant's arguments are found persuasive and therefore, the objection is withdrawn.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Amended claims 1 and 8 recite "combining cell fractions". Amended claims 9 and 10 recite "combined cell fractions". The specification does not provide literal support for this recitation. The specification also does not provide figurative support for this recitation. The specification teaches a method that encompasses a series of isolation step that gradually provide a distinct enriched population of cardiomyocytes. However, the amendment to the claim now encompasses the combination of factions that bring out a more heterogeneous population of cells, which is not supported by the specification.

Amended claim 1 also recites, "culturing the initiated cells so that they differentiate", which broadens the scope of the original claim, which recited "culturing the initiated cells so that they differentiate into areas that undergo spontaneous contraction". The specification does not provide support for cells that differentiate into any cell type but only provides for cells that differentiate to display the distinct phenotype of undergoing spontaneous contraction. Therefore, the specification does not provide figurative support for the broader embodiment encompassed by the amendment to claim 1.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1-10 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

As stated above, the amendment to the claims encompasses cells that differentiate into any cell type. However, the specification supports cell that differentiate to display spontaneous contraction. This specific phenotype of spontaneous contraction is the first marker by which cells are isolated and identified to contain cardiomyocytes and therefore an essential step in the method of the invention. The art teaches us that human embryonic stem cells can differentiate into multiple lineages. If a differentiated cell population is selected that is not undergoing spontaneous contraction, as is encompassed by the claims, it is not clear from the specification that end product will

result in the cell composition of cardiomyocytes as claimed. Therefore, an artisan would not know to use the instant invention to produce a cell composition of cardiomyocytes as claimed. (This issue of enablement is discussed in more detail under the scope of enablement rejection.)

Scope of Enablement

7. Claims 1-10 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating cardiomyocytes or cardiomyocytes precursor cells from human embryonic stem (hES) cells obtained from a human blastocyst comprising initiating differentiation of the hES by forming embryoid bodies (EB) in suspension culture, wherein differentiated cells of the EB undergo spontaneous contraction, harvesting the differentiated cells that demonstrate spontaneous contraction, further separating the harvested cells into factions by density centrifugation, and isolating the cells that express cardiac tronin I (cTnI), cardiac troponin T (cTnT), atrial natriuretic factor (ANF) or α-cardiac myosin heavy chain (MHC), thereby generating a cell composition comprising cardiomyocytes or cardiomyocytes precursors, does not reasonably provide enablement for a method comprising initiating differentiation of any pPS cell, collecting any differentiated cells and generating a cell composition containing cardiomyocytes or cardiomyocytes precursor cells only.

Applicant traversed the scope of enablement rejection set forth in the office action mailed 7/13/2006 on the grounds the amendments to the claims to recite hES

cells overcome the rejection and that the claims use the word "containing" and therefore the claims to not require a homogenous population of cardiomyocytes.

Applicant's arguments are not found persuasive, first, because the recitation of hES cells does not correct for all the enablement issues introduced by the amendment to the claims. The amendments to the claims no longer require the harvesting differentiated cells that undergo spontaneous contraction and now rely solely on isolating cardiomyocytes with the use of cardiac specific markers cTnI, cTnT, and ANF. However, the methods taught in the specification rely upon the isolating of beating cells from the embryonic bodies before the enrichment step of centrifugation and characterization by cardiac specific markers. Example 2 (p. 26-27) isolates cardiomyocytes solely by isolating beating cells from embryoid body outgrowths and does not use the cardiac specific marker at all. Example 3 (p. 27-29) further characterizes the isolated cells by immunofluorescence using the cardiac specific markers to further provide evidence that the cells isolated by the method of Example 2 are express markers known to be present in cardiomyocytes. Example 4 (p. 29-30) teaches a method of enriching the cardiomyocytes population of cell by further subjecting the beating cells that were harvested from the embryoid body culture to gradient centrifugation and then further characterized the beating cells in the fractions with the myosin heavy chain cardiac specific marker. Overall, in all of the disclosed method of the specification is it the harvesting of the cell that undergo spontaneous contraction from the embryoid bodies that results in the cell composition of cardiomyocytes, not the use of the cardiac specific markers to isolate the cell

composition of cardiomyocytes. Therefore, the harvesting of the differentiated cells that undergo spontaneous contractions is an essential step in the method.

Furthermore, the use of cardiac specific markers solely to isolate the differentiated cells would not result in a cell composition comprising cardiomyocytes and cardiomyocytes precursors as claimed. As disclosed in the specification, cardiac specific markers are a descriptive means of demonstrating that cells are expressing proteins most commonly found in cardiac cells and cardiomyocytes. However, it does not demonstrate that the cells in the composition function as cardiomyocytes. Therefore, it is possible the differentiated cells isolated by the claimed method have characteristics of cardiomyocytes as demonstrated by the expression of the cardiac specific markers but do not function as cardiomyocytes because the cells were not spontaneously contracting cells. Furthermore, the breadth of the instant claims now encompass the harvesting of any differentiated cell, contracting and non-contracting. It is well established in the art the hES cell differentiate into multiple linages other than cardiomyocytes. Therefore, many of the harvested cells would not be of cardiomyocytes linage. Overall, an artisan would not know how to use the instant method to produce a cell composition of cardiomyocytes as claim with the use of cardiac specific markers solely and without the harvesting of the spontaneously contracting or beating cells.

Applicant second argument that the claims use the word "containing" and therefore the claims to not require a homogenous population of cardiomyocytes is also not found persuasive. It is acknowledged that the "containing" allows for other factors to

be present and therefore would not require a fully homogenous population. However, one of the intended uses for the cardiomyocytes cell composition is in human cardiac therapy and cardiac engraftment. If the cardiomyocytes cell composition produced by the instantly claimed method was not a relatively homogenous composition of cardiomyocytes, it is not clear that the engraftment would provide the quantity and quality of cells necessary for a successful engraftment.

Therefore, because the amendments to the claims and Applicant's arguments do not rectify the existing enablement issues and the amendments introduce new enablement issues, the instant scope of enablement rejection is maintained.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-16, rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the broad recitation "primate pluripotent stem (pPS) cells", and in the same the claim recites "obtained from a human blastocyte", which is the narrower statement of the range/limitation, has been amended and no longer encompasses the broad and narrow limitations together in the same claim. Therefore, the rejection is withdrawn.

Claims 3 and 4, deemed indefinite for their recitation of the phrase "such as", has been amended and no longer contains with recitation. Therefore, the rejection is withdrawn.

Claims 6 and 13, deemed indefinite in their recitation of the relative term "about", has been amended to no longer recite this recitation. Therefore the rejection is withdrawn.

Claims 1 and 8, deemed indefinite for their recitation of "according to", has been amended and no longer recites this recitation. Therefore, the rejection is withdrawn.

Claims 9 and 10, deemed to lack sufficient antecedent basis for their recitation "the collected cells", has been amended and no longer recites this recitation. Therefore, the rejection is withdrawn.

Claim 2 stands rejected for its recitation of the trademark Matrigel™. Applicant traversed this rejection on the grounds that Examiner did not provide a sufficient argument for the recitations indefinitness and states that the MPEP allows for claiming trademarks. Applicant's argument are not found persuasive because in the instant case the recitation of "Matrigel" is indefinite because not all the components are Matrigel are known and are subject to change, revision, and improvement by the manufacturers of Matrigel. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 11-16, rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al. (Circ Res 91:501-508, 2002; of record), is withdrawn.

Claims 11-16 have been canceled, therefore the rejection of these claims is rendered moot and therefore withdrawn.

Applicant traverse the rejection of claim 1 because it receives benefit of priority to an earlier provisional application with a filing at of 7/12/2001and therefore Xu et al can not be used as prior art. Applicants arguments are found persuasive and therefore the rejection of claim 1 is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, and 6-10, rejected under 35 U.S.C. 103(a) as being unpatentable over Doevendans et al (J Mol Cell Cardiol 32:839-851, 2000, of record), Sugi and Lough (Dev Biol 168:567-574, 1995; of record), Murrell et al. (Mech Aging Dev 77(2):abstract, 1994) Takahashi et al (J Cardio Pharm 41(5): 726-733), Nair and Nair (Indian J Exp Biology 35(5):abstract) and (Makino et al. J clin Invest 103(5):697-705), in view of Kehat et al (J Clin Invest 108(3):407-414, 2001, of record), is withdrawn.

Applicant traversed this rejection on the grounds that Kehat et al can not be considered prior art because it was published in Aug of 2001 and the instant claims received benefit of an earlier filing date of 7/12/2001. Applicant argues that without this art the rejection does not provide a reasonable expectation of success. Applicant's arguments are found persuasive because although the instant methods have been established in mouse ES cells this provides motivation but not a reasonable expectation of success and furthermore, because producing cell composition of a specific cell type of ES cells is unpredictable in the art, it is not clear the methods disclosed in the art would be directly applicable to hES at the time of filing. Therefore, the rejection is withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 2, 4, 7, 8 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-12 of copending Application No. 11/086,709. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions have overlapping scope.

Applicant states that the instant rejection is provisional and if copending application becomes allowable prior to allowance of the current claims, Applicant will address the rejection on their merits or will file a terminal disclaimer. Applicant's statement is acknowledged and the rejection is maintained.

12. Claims 1-5, 7, 8, 10 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12-18, and 20 of copending Application No. 11/040691

Applicant states that the instant rejection is provisional and if copending application becomes allowable prior to allowance of the current claims, Applicant will address the rejection on their merits or will file a terminal disclaimer. Applicant's statement is acknowledged and the rejection is maintained.pping scope.

13. Claims 1, 2, 6-8 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 and 16 of copending Application No. 11/085,899. Although the conflicting claims are not identical, they are not patentably distinct from each other because they have overlapping scope.

Applicant states that the instant rejection is provisional and if copending application becomes allowable prior to allowance of the current claims, Applicant will address the rejection on their merits or will file a terminal disclaimer. Applicant's statement is acknowledged and the rejection is maintained.

14. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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